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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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LETTERS TO THE EDITOR

What Is Inherited in the Predisposition to Alcoholism: New Model or More Muddle?

Begleiter and Porjesz (1999) advanced a "speculative" formulation of alcoholism liability based on a synthesis of evidence drawn from neurobiological, genetic, and behavioral research. The central thesis is that "an innate imbalance of excitation/inhibition" underlies the risk for alcoholism.

It is consensually accepted that sound theory guides innovative research; however, the quality of a theory is judged according to its explanatory and predictive power. Employing these latter criteria, the extant empirical literature does not support the model proposed by Begleiter and Porjesz.

A central proposition is that low P3 amplitude is a neurophysiological endophenotype reflecting the genetic risk for alcoholism. Although not acknowledged by Begleiter and Porjesz, it should be emphasized that *many studies have documented a P3 amplitude diminution in individuals at familial high risk for neuropsychiatric disorders that are genetically unrelated to alcoholism.* These disorders include schizophrenia (Blackwood et al., 1991), bipolar affective disorder (Squires-Wheeler et al., 1993), and Alzheimer disease (Boutros et al., 1995). Thus, attenuated P3 amplitude has very little, if anything, to do with *specifically* the etiology of alcoholism. Hence, gene loci and genetic variance claimed to underlie the P3 phenotype are related to a broad and genetically heterogeneous spectrum of neuropsychiatric disorders, including disorders genetically unrelated to alcoholism.

The P3 studies reviewed to support the model proposed by Begleiter and Porjesz only reveal mean group differences according to group membership (e.g., affected versus nonaffected). Critically missing from their literature review is documentation regarding the *sensitivity* of P3 voltage for detecting true positives; that is, persons at known high risk for alcoholism (or already affected). Also missing is information about the *specificity* of the P3; that is, its capacity to identify true negatives, namely, individuals who are not at designated high risk or have no history of affectedness. *In the absence of this type of discriminative analysis, the claim by Begleiter and Porjesz that an attenuated P3 is "characteristically" observed in alcoholics, their relatives, and their offspring is a misleading exaggeration.* The critical question is: What percent of biological first-degree relatives of alcoholics and nonalcoholics have low and high P3 amplitude, respectively? Inasmuch as Dr. Begleiter is the principal investigator of the prestigious Collaborative Genetic Study of Alcoholism, where a large sample is present, his long-argued position regarding the salience of the P3 as a marker for alcoholism can be definitively and expeditiously determined.

A significant genetic correlation between P3 amplitude and alcoholism diagnosis cited in that article (−0.71) could be a strong argument for the utility of P3 in the search for alcoholism-related genetic loci. However, because the bivariate genetic data were obtained in a sample that included affected individuals with varying severity of alcoholism, *the genetic correlation can only be accepted in their argument if it is proven that alcoholism is not causal to the diminished P3.* Notably, Begleiter and Porjesz state: "evidence that increased severity of alcohol dependence is inversely related to P3 amplitude." This statement is consistent with a conclusion that alcoholism impacts on the P3 amplitude. It also is consistent with a conclusion that the low P3 voltage reflects (at least in part) permanent cortical dysfunction as has been observed in neuroimaging and neuropsychological research. *The point to be made is that including affected individuals in the linkage analysis, using a phenotype such as P3 that covaries with alcohol dependence, confounds the genetic correlation claimed by Begleiter and Porjesz.* Similarly, the claim from COGA data pointing to a tentative QTL at the alcohol dehydrogenase ADH3 region employing a bivariate linkage analysis of P3 and alcoholism (Williams et al., 1999) can be explained by the same cause-effect relationship noted above. In effect, it is more plausible to infer that the ADH3-P3 connection is *secondary* to the ADH3-alcoholism connection in contrast to the argument by Begleiter and Porjesz that the ADH3 gene is related to the P3. For Begleiter and Porjesz to advance a convincing argument, it is necessary to document P3 in naïve individuals who become alcoholic and then use these subjects as probands in linkage analyses. The observation that P3 amplitude decrements are found in abstinent alcoholics does not offset the possibility of irreversible changes in brain electrophysiology consequent to chronic alcoholism.

It is generally accepted that early age onset alcoholism is the culmination of a deviant ontogenetic trajectory (Tarter and Vanyukov, 1994). Begleiter and Porjesz propose that the ADHD and CD in childhood are precursor outcomes to alcoholism. Significantly, Bauer and Hesselbrock (1999) conclude from their research that "P300 decrements previously attributed to familial alcohol/substance dependence might be the result of a coincident increase in the prevalence of conduct problems." Inasmuch as alcoholism emerges from ADHD and CD in the Begleiter and Porjesz model, it is also significant to note that *no evidence is provided to suggest that alcoholism is not merely the probable outcome of behaviorally deviant development and a socially non-normative adjustment style established prior to drinking*

onset. Because ADHD/CD are proposed to be the first illnesses observed in ontogenesis, their research could be more productive by studying children with these latter antecedent disorders. Without specification of any factors specific to alcoholism, the model relegates alcoholism to a group of developmental outcomes of deviancy that also includes trauma injury, STD/HIV, and unplanned pregnancy.

Antisociality is hypothesized by Begleiter and Porjesz to be presaging as well as comorbid to alcoholism. Significantly, nicotine, caffeine, cocaine, and amphetamine consumption is prevalent among antisocial alcoholics. No discussion is provided by the authors that suggests why these *stimulants* would be habitually used if alcohol is consumed to provide "initial relief from hyperexcitability" (Begleiter and Porjesz, 1999, Fig. 2, p. 1132). According to the Begleiter and Porjesz model, exacerbating brain excitability by stimulant drug consumption would comprise a punishment.

It is notable that substantial evidence pertaining to ADHD (a developmental endophenotype preceding alcoholism in the Begleiter and Porjesz model) points to physiologic underarousal—not hyperexcitability. For example, Lahey et al. (1988) define a subtype of ADHD featured by sluggishness, daydreaming, and drowsiness. Notably, in the APA field trials (APA, 1994) drowsiness and daydreaming had positive predictive utility. Not surprisingly, therefore, stimulant drugs are therapeutically effective inasmuch as they elevate arousal to an optimum level. Considering this body of evidence, in conjunction with the frequent observation that novelty seeking and risk taking behavior are also common in ADHD/CD youth who are at risk for alcoholism, a convincing argument can be advanced to implicate CNS hypoarousal.

The notion proffered by Begleiter and Porjesz that homeostatic imbalance results in "excess" CNS excitability is engaging. However, the authors do not acknowledge the important prior theoretical contributions of Eysenck (1967), Gray (1964), Pavlov (1927), and Zuckerman (1979) as well as others who have catalyzed a rich line of scientific inquiry pertaining to the association between an excitation/inhibition imbalance and psychological functioning. A consideration of the findings from this literature by Begleiter and Porjesz would have yielded a balanced and informative conceptualization.

In summary, the need for innovative models and theories is universally recognized. The shortcomings of the model proposed by Begleiter and Porjesz pertain to the absence of genetic and phenotypic factors that specifically pertain to alcoholism. The notion that P3 voltage is an endophenotype that is characteristic of individuals at known high risk remains unsubstantiated. The notion that the genetic underpinnings of the P3 pertain to alcoholism does not coincide with findings that this ERP component is also associated with neuropsychiatric disorders that are genetically unrelated to alcoholism. The reported significant genetic correlations in the linkage analysis are likely confounded by the influence of a chronic history of alcoholism on the P3 amplitude phenotype. Furthermore, the drug preferences of antisocial alcoholics and the pharmacotherapeutic response of ADHD children to stimulant drugs do not concur with the notion that a state of brain hyperexcitability is the physiologic disorder prodromal to clinical alcoholism.

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REFERENCES

Am Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).* American Psychiatric Press, Washington, D.C.

Bauer L, Hesselbrock V (1999) P300 decrements in teenagers with conduct problems: Implications for substance abuse risk and brain development. Biol Psychiatry 46:263–272.

Begleiter H, Porjesz B (1999) What is inherited in the predisposition toward alcoholism? A proposed model. Alcohol Clin Exp Res 23:1125–1135.

Blackwood D, St. Clair D, Muir W, Duffy J (1991) Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. Arch Gen Psychiatry 48:899–909.

Boutros N, Wu S, Torello M, Nasrallah H, Burns E (1995) Evoked potentials in subjects at risk for Alzheimer's disease. Psychiatry Res 57:57–63.

Eysenck HJ (1967) *The Biological Basis of Personality.* Charles C Thomas, Springfield.

Gray J (1964) Strength of the nervous system and levels of arousal: A reinterpretation, in *Pavlov's Typology* (Gray J ed), Macmillan, New York.

Lahey B, Pelham W, Schaughency E, Atkins MS, Murphy HA, Hynd G, Russo M, Hartdagen S, Lorys-Vernon A (1988) Dimensions and types of attention deficit disorder. J Am Acad Child Adolesc Psychiatry 27:718–723.

Pavlov J (1927) *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex* (Translated by G. Anrep). Oxford University Press, Oxford.

Squires-Wheeler E, Friedman D, Skodal A, Erlemeyer-Kimling L (1993) A longitudinal study relating P3 amplitude to schizophrenia spectrum disorders and to global personality functioning. Biol Psychiatry 33:774–785.

Tarter R, Vanyukov M (1994) Alcoholism: A developmental disorder. J Consult Clin Psychol 62:1096–1107.

Williams JT, Begleiter H, Porjesz B, Edenberg HJ, Foroud T, Reich T, Goate A, Van Eerdevegh P, Almasy L, Blangero J (1999) Joint multipoint linkage analysis of multivariate qualitative and quantitative traits: II. Alcoholism and event-related potentials. Am J Hum Genet 65:1148–1160.

Zuckerman M (1979) *Sensation Seeking Beyond the Optimal Level of Arousal.* Lawrence Erlbaum Associates, Hillsdale.

Response

Begleiter and Porjesz (1999) fully acknowledge that "the speculative formulation" advanced in our paper is not ubiquitous to all alcohol-dependent individuals, and this is explicitly stated. A thorough reading and understanding of the literature can readily dispense with all of the arguments raised by Tarter (1999).

We have repeatedly stated in the literature, (most recently Almasy et al., 1999; Williams et al., 1999), that the P3

deficits observed in alcoholics and individuals at high risk to develop alcoholism are not specific to alcoholism, but are found in schizophrenic patients, and as stated in our recent publication (Begleiter and Porjesz, 1999), are also present in individuals with substance abuse (Bauer 1997; Brigham et al., 1997), antisocial personality (Bauer et al., 1994; O'Connor et al., 1994), and attention deficit hyperactivity disorder (Herning and King, 1996). In fact, we have published observations of low P3s in schizophrenics (Brecher and Begleiter, 1983; Brecher et al., 1987a,b).

We disagree with Tarter regarding the issue of *sensitivity*, and have published data on sensitivity using Z-score distributions (Porjesz et al., 1998), and more recently, heritability of the P300 component of the ERP (Almasy et al., 1999). Both these papers were cited in our manuscript. We take issue with Tarter's statement that "the P3 studies reviewed to support the model proposed by Begleiter and Porjesz only reveal *mean* group differences according to group membership (e.g., affected versus nonaffected)." We have addressed this issue in the paper cited above (Porjesz et al., 1998) which was published in *Alcoholism: Clinical and Experimental Research* (Vol 22, No 6), in which we compare *distributions* of P3 amplitude—not just mean amplitudes—between members of densely affected alcoholic families and "randomly" ascertained control families. These comparisons were performed on age and sex-matched groups, using Z-score distributions. In that article, we not only reported mean differences between affected and nonaffected individuals, high-risk versus low-risk, unaffected relatives and controls, but also found that significantly more individuals from densely affected families manifested P3s at the low end of the distribution than did individuals from "randomly" ascertained control families. Importantly, we reported that this significant difference in the distribution of P3 amplitude between dense and random families was found in all age- and sex-matched comparisons—between offspring, affected, and unaffected individuals from these families—and we reported these percentage differences. Therefore, we feel we have addressed the "critical question" raised by Tarter, namely, "What percent of biological first-degree relatives of alcoholics and nonalcoholics have low and high P3 amplitude, respectively?" Similarly, a comparison of the high end of the distributions of P3 indicates that significantly more individuals from control families are represented compared with individuals from the densely affected families. Again, this is true when we compare affected or unaffected individuals from the control and densely affected families. While affected individuals in densely affected families manifest lower P3s than unaffected individuals from these families, *affected* individuals in our random control families do not manifest lower P3s than their unaffected relatives. Therefore, the P3 amplitude does not simply reflect the effects of alcoholism per se.

We have asserted the importance of using broader approaches, such as related biological variables, to identify pertinent phenotypes in nonaffected subjects carrying vulnerability genes. The biological endophenotypes are extremely useful to identify relatives of affected individuals who, on the basis of conventional diagnostic criteria, would be considered unaffected, but who nevertheless are at risk for the disease. It is important to note that because the disease involves the interaction of multiple genes, the biological endophenotypes need not be disease-specific.

Tarter argues that the genetic correlation we have observed can only be accepted "if it is proven that alcoholism is not causal to the diminished P3." That this is very much the case is the "raison d'être" for the use of P3 as an endophenotype. Our initial article (Begleiter et al., 1984) demonstrated unequivocally that *naive* young sons of chronic alcoholics manifested a significantly reduced P3 compared with controls. It was clearly stated in our article that all the subjects were selected because they had no experience with alcohol or any illicit drugs. Needless to say, this finding has been replicated a number of times, including at Tarter's own institution (Hill and Steinhauer, 1993), and has been the subject of a meta-analysis (Polich et al., 1994) which clearly identified a significant observation across many studies. Studies of the acute effects of alcohol on P3s indicate that it affects P3 *latency* more than amplitude (Porjesz and Begleiter, 1993; Schuckit et al., 1988). Furthermore, alcoholics who are abstinent for prolonged periods still manifest low P3s (Porjesz and Begleiter, 1985) (this latter finding was published in a book edited by Tarter). Thus P3 amplitude represents a *"trait"* rather than a "state" marker.

The importance of risk in contrast to exposure to alcohol was elegantly demonstrated by Pfefferbaum et al. (1991) who reported that in abstinent alcoholics, P3 amplitude reflects family history but not alcohol consumption; similar findings have been noted by other investigators (Benegal et al., 1995; Cohen et al., 1995). This well established observation provides a compelling argument for the relationship between P3 amplitude and family history of alcoholism and not alcohol intake. Three additional studies provide strong evidence for the role of diminished P3 in young boys and the subsequent abuse of alcohol and/or illicit substances (Berman et al., 1993; Hill et al., 1995; Iacono, 1998).

Tarter is under a misconception regarding the Williams et al. (1999) results, when he states that "the ADH3–P3 connection is *secondary* to the ADH3-alcoholism connection *in contrast to the argument by Begleiter and Porjesz that the ADH3 gene is related to the P3* " (italics added). In fact, we clearly state that this region on chromosome 4 "strongly influenced liability to alcoholism. . . with evidence for pleiotropic effects on P3 (Begleiter and Porjesz, 1999, p1129)." Thus we never state that the ADH3 gene is directly related to P3, as Tarter claims.

Tarter states, "Without specification of any factors specific to alcoholism, the model relegates alcoholism to a group of developmental outcomes of deviancy..... " Tarter confuses *predisposing risk factors* that increase the

probability of a given outcome (alcohol dependence) with factors that *predetermine* outcome. We certainly do not believe that possessing (identifying) these predisposing factors necessarily determines destiny, and we reaffirm our position that these risk factors, although not specific to alcoholism, increase the risk. Tarter states that the Begleiter and Porjesz (P3) model asserts that "alcoholism emerges from ADHD and CD." However, a close inspection of Fig. 2 in our article (Begleiter and Porjesz, 1999; p. 1132) would readily reveal that there are at least two pathways that may contribute to the development of alcoholism: One is the contribution of externalizing disorders, the other is the direct contribution of disinhibition/CNS hyperexcitability. Both pathways are clearly illustrated in our schematic chart of the proposed model, but conveniently overlooked by Tarter.

Tarter asserts that nicotine, caffeine, cocaine, and amphetamine consumption is prevalent among individuals with antisocial personality disorder (ASP). Indeed, it should be noted that according to the ECA study, by far the most abused drug among ASP individuals is alcohol (Regier et al., 1990). Moreover, the most prevalent comorbid condition with alcohol dependence is Antisocial Personality Disorder (ASPD).

On the issue of ADHD, Tarter argues that this clinical condition represents a state of under-arousal treated effectively with stimulant drugs. It is correct that most evidence suggests a primary role of the dopaminergic system in ADHD. However, it is important to note that converging evidence implicates the dopaminergic system and the nigrostriatal regions in the pathophysiology of ADHD. Indeed, Tarter offers a gratuitous contradiction when he describes attention deficit *hyperactivity* disorder as a condition with *physiologic underarousal.*

In studies conducted by Ernst and colleagues at NIH, the authors conclude that only the prefrontal cortex demonstrated significantly different F18 - DOPA ratio in ADHD compared with controls (Ernst et al., 1998). The prefrontal cortex is well known to have inhibitory functions, which when deficient, produces hyperexcitability as reflected by inattention and excessive motor activity. Furthermore, it should be noted that the alcohol dependence literature is replete with scientific observations noting the early incidence of ADHD followed by the subsequent development of alcoholism.

In discussing the imbalance between excitation and/inhibition proposed in our model, Tarter does not distinguish between physiologic and psychological disinhibition. It should be noted that we are proposing a state of *physiologic* disinhibition, and it cannot be assumed that this underlying physiologic imbalance necessarily leads to behavioral disinhibition. Tarter concedes that our proposed model asserting homeostatic imbalance resulting in "excess" CNS excitability might have had some merit had we cited the prior contributions of Eysenck (1967), Gray (1964), Pavlov (1927), and Zuckerman (1979). He concludes by stating that citing the aforementioned literature "would have yielded a balanced and informative conceptualization." We are most puzzled by this statement which purports that a citation of a few references would suddenly provide our proposed model with a balanced and informative conceptualization.

We do not propose this model with the firm conviction that it is "right" or "wrong," but believe that it will yield a number of testable hypothesis that can further our understanding of etiologic factors in alcohol dependence. The *model* we have proposed is not a *theory,* but a tentative description of a system. It is no more than a paradigm, which according to the pre-eminent philosopher of science Kuhn (1962) is described as essentially a collection of beliefs. According to Kuhn (1962), paradigms are essential to scientific inquiry; it guides the research efforts of scientific communities, and it is this criterion that most clearly identifies a field as a science. Finally, it should be noted that the typical developmental pattern of a mature science is the successive transition from one paradigm to another through a process of evolution.

It is our hope that the model or paradigm we propose will either live up to scientific scrutiny or will result in a paradigm shift.

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REFERENCES

Almasy L, Porjesz B, Blangero J, Chorlian DB, O'Connor SJ, Polich J, Kuperman S, Rohrbaugh J, Bauer LO, Reich T, Begleiter H (1999) Heritability of the P300 and N100 components of the even-related brain potential in families with a history of alcoholism. Psychiatr Genet 88:383–390.

Bauer LO (1997) Frontal P300 decrements, childhood conduct disorder, family history, and the prediction of relapse among abstinent cocaine abusers. Drug Alcohol Depend 44:1–10.

Bauer LO, O'Connor SO, Hesselbrock VM (1994) Frontal P300 decrements in antisocial personality disorder. Alcohol Clin Exp Res 18:1300–1305.

Begleiter H, Porjesz P (1999) What is inherited in the predisposition toward alcoholism? A proposed model. Alcohol Clin Exp Res 23:1125–1135.

Begleiter H, Porjesz B, Bihari B, Kissin B (1984) Event-related potentials in boys at risk for alcoholism. Science 225:1493–1496.

Benegal V, Jain S, Subbukrishna DK, Channabasavanna SM (1995) P300 amplitudes vary inversely with continuum of risk in first degree male relatives of alcoholics. Psychiatr Genet 5:1–8.

Berman MS, Whipple SC, Fitch RJ, Noble EP (1993) P3 in young boys as a predictor of adolescent substance abuse. Alcohol 10:69–76.

Brecher M, Begleiter H (1983) Event-related brain potentials to high-incentive stimuli in unmedicated schizophrenic patients. Biol Psychiatry 18:661–674.

Brecher M, Porjesz B, Begleiter H (1987) Late positive component amplitude in schizophrenics and alcoholics in two different paradigms. Biol Psychiatry 22:848–856.

Brecher M, Porjesz B, Begleiter H (1987) The Nw component of the event-related potential in schizophrenic patients. Electroencephalogr Clin Neurophysiol 66:369–375.

Brigham J, Moss HB, Murrelle EL, Kirisci L, Spinelli JS (1997) Event-related potential negative shift in sons of polysubstance-and alcohol-use dosorder fathers. Psychiatry Res 73:133–146.

Cohen HL, Wang W, Porjesz B, Begleiter H (1995) Auditory P300 in young alcoholics: Regional response characteristics. Alcohol Clin Exp Res 19:469–475.

Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM (1998) DOPA decarboxylase activity in attention deficit hyperactivity disorder in adults: A (fluorine-18) fluorodopa positron emission tomographic study. Neuroscience 18:5901–5907.

Eysenck HJ (1967) *The Biological Basis of Personality*. Charles C Thomas, Springfield.

Gray J (1964) Strength of the nervous system and levels of arousal: A reinterpretation, in *Pavlov's Typology* (Gray J ed), Macmillan, New York.

Herning RI, King DE (1996) EEG and evoked potentials alterations in cocaine-dependent individuals. NIDA Res Monogr 163:203–223.

Hill SY, Steinhauer SR (1993) Assessment of prepubertal and post pubertal boys and girls at risk for developing alcoholism with P300 from a visual discrimination task. J Stud Alcohol 54:350–358.

Hill SY, Steinhauer S, Locke J (1995) Event-related potentials in alcoholic men, their high-risk male relatives, and low-risk male controls. Alcohol Clin Exp Res 19:567–576.

Iacono WG (1998) Identifying psychophysiological risk for psychopathology: Examples from substance abuse and schizophrenia research. Psychophysiology 35:621–637.

Kuhn T (1962) *The Structure of ScientificRrevolutions*. University of Chicago Press, Chicago.

O'Connor SJ, Bauer L, Tasman A, Hesselbrock V (1994) Reduced P3 amplitudes are associated with both a family history of alcoholism and antisocial personality disorder. Prog Neuropsychopharmacol Biol Psychiatry 18:1307–1321.

Pavlov J (1927) *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex* (Translated by G. Anrep). Oxford University Press, Oxford.

Polich J, Pollock VE, Bloom FE (1994) Meta-analysis of P300 amplitude from males at risk for alcoholism. Psychol Bull 115:55–73.

Porjesz B, Begleiter H (1985) Human brain electrophysiology and alcoholism, in *Alcohol and the Brain* (Tarter R, Thiel DV, eds), pp 139–182, Plenum, New York.

Porjesz B, Begleiter H (1993) Neurophysiological factors associated with alcoholism, in *NIAAA Research Monograph No. 22, Alcohol-Induced Brain Damage* (Nixon SI, Hunt WA, eds), pp 89–120, NIAAA, Rockville.

Porjesz B, Begleiter H, Reich T, Van Eerdewegh P, Edenberg HJ, Foroud T, Goate A, Rice J, Litke A, Chorlian D, Blangero J, Stimus AT, Sorbell J, Bauer LO, Kuperman S, O'Connor SJ, Rohrbaugh J (1998) Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism: Preliminary results from the COGA project. Alcohol Clin Exp Res 22:1317–1323.

Regier DA, Farmer M, Rae D, Locke B, Keith S, Judd L, Goodwin FK (1990) Comorbidity of mental disorders with alcohol and other drug abuse. JAMA 264:2511–2518.

Schuckit MA, Gold EO, Croot K, Finn P, Polich J (1988) P300 latency after ethanol ingestion in sons of alcoholics and controls. Biol Psychiatry 24:310–315.

Tarter RE (2000) Response to Begleiter and Porjesz: What is Inherited in the Predisposition to Alcoholism: New Model or More Muddle? Alcohol Clin Exp Res 24:246.

Williams JT, Begleiter H, Porjesz B, Edenberg HJ, Foroud T, Reich T, Goate A, Van Eerdewegh P, Almasy L, Blangero J (1999) Joint multipoint linkage analysis of multivariate qualitative and quantitative traits: II. Alcoholism and event related potentials. Am J Hum Genet 65:1148–1160.

Zuckerman M (1979) *Sensation Seeking Beyond the Optimal Level of Arousal*. Lawrence Erlbaum Associates, Hillsdale.